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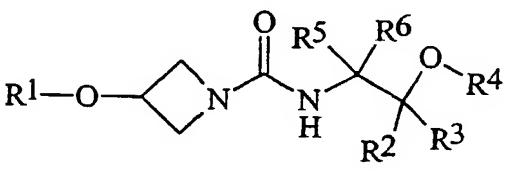
(54) Title: AZETIDINE CARBOXAMIDE DERIVATIVES FOR THE TREATMENT OF CNS DISORDERS



(I)

(57) Abstract: Use of a compound of formula (I) wherein R^1 is aryl; and R^2, R^3, R^4, R^5 and R^6 which may be the same or different are selected from H, alkyl and aryl, or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for neuroprotection in a subject or for the treatment of cerebral ischaemia, central nervous system injury or eye diseases.

AZETIDINE CARBOXAMIDE DERIVATIVES FOR THE TREATMENT OF CNS DISORDERS

The present invention relates primarily to neuroprotection and to the treatment of stroke and other cerebrovascular disorders.

Stroke and other acute brain injuries are major causes of mortality and morbidity in the adult population. Stroke is the third highest cause of death in major industrialised countries and the commonest cause of permanent disability. Each year, in the US and Europe, approximately 1 million people suffer an acute stroke. Between 25% and 35% of these patients die within the first three weeks, and of the survivors 25% to 50% will be totally dependant on family or institutional care for the rest of their lives. The incidence of stroke increases with age, roughly doubling with each passing decade, with 30% of persons aged over 65 years being affected.

The statistics for stroke translate into an annual incidence of 0.1 to 0.2% in the US and Europe, with the world-wide market for stroke estimated to be worth $3 billion in 1995 and projected to rise to $10 billion in 2005. There is an unmet medical need for a cytoprotective therapy for stroke.

No effective neuroprotectant therapy is presently available for cerebrovascular disorders. The only therapy currently licensed for the treatment of ischaemic stroke is Genetech's thrombolytic recombinant tissue plasminogen activator (Activase®, rtPA; Alteplase). Activase is indicated for the management of acute ischaemic stroke in adults for improving neurological recovery and reducing the incidence of disability. Treatment with Activase should only be initiated within 3 hours after the onset of stroke symptoms, and after exclusion of intracranial haemorrhage by a cranial computerised tomography (CT) scan or other diagnostic imaging method sensitive for the presence of haemorrhage.

The mechanisms underlying the irreversible brain damage which occurs following ischaemia are complex. Many classes of compounds are currently under investigation as treatments for cerebrovascular disorders. Acute intervention with both cytoprotective (neuroprotective) and other thrombolytic agents is undergoing active investigation.

Cytoprotective neuroprotective therapy includes drugs that act to prevent cell death during ischaemia and reperfusion. These agents include calpain inhibitors, voltage-sensitive calcium- and sodium-channel antagonists, receptor-mediated calcium-channel antagonists [including *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) antagonists], glutamate-synthesis inhibitors, glutamate-release antagonists, γ-aminobenzoic acid (GABA) antagonists, 5-HT (serotonin) receptor agonists, gangliosides, antioxidants, growth factors, antiapoptotic agents, and antiadhesion molecules (Silver, B., Weber, J., Fisher, M., *Clin. Neuropharmacol.* **1996**, *19*, 101-128).

Excitotoxicity is a major determinant of neuronal death following the induction of cerebral ischaemia. Repetitive cell firing, persistent depolarisation and induction of supra-normal ionic flux across excitable membranes can initiate fatal cellular compromise *via* a variety of synergistic mechanisms during hypoxic excitotoxicity. Control of the state of excitability of neurons depends upon the net balance of excitatory and inhibitory influences acting on that neurone.

In general, the primary excitatory influence impinging on neurones is mediated by the glutamatergic system, whilst primary inhibition is frequently determined by GABAergic innervation, since the main endogenous inhibitory amino acid in mammalian brain is GABA. Thus increasing the inhibitory effect of GABAergic innervation, and decreasing the excitatory influence of glutamate, will reduce the net excitation of a neurone. Reducing excitation will reduce the consequences of energy depletion due to hypoxia and promote the ability of the neurone to survive hypoxic cerebral ischaemia.

Relatively few of the drugs currently under investigation as neuroprotectants for the treatment of stroke and other cerebrovascular disorders are modulators of the endogenous inhibitory amino acid, GABA.

One class of molecules which apparently possess neuroprotective properties is the GABA uptake inhibitors such as CI-966, which was shown to be effective in a gerbil ischaemia model utilising global cerebral ischaemia of 5 min. duration (Phillis, J.W., *Gen. Pharmacol.* **1995**, *26*, 1061-1064).

The benzodiazepine receptor agonist diazepam has been shown to possess some neuroprotective properties (Karle, J., Witt, M. R., Nielsen, M., *Brain Res.* **1997**, *765*, 21-29).

In rabbits with reversible spinal cord ischaemia, treatment with muscimol, a reference $GABA_A$ agonist, at 5 mg/kg significantly prolonged P_{50} time, where P_{50} represents the duration associated with 50% probability of resultant permanent paraplegia (Madden, K.P., *Stroke*, **1994**, *25*, 2271-2275).

Felbamate, an antiepileptic drug with *inter alia* GABA agonist properties, provided significant neuronal protection when administered both before and after ischaemia in all regions of the brain in the gerbil model of transient forebrain ischaemia. Protection was moderate when felbamate was used before ischaemia, but was highly significant when felbamate was given 30 min. after the insult. The structural protection with felbamate was very significant when used in the post-ischaemic period (Shuaib, A., Waqaar, T., Ijaz, M.S., Kanthan, R., Wishart, T., Howlett, W., *Brain Res.* **1996**, *727*, 65-70).

Piracetam is a derivative of GABA, and was the first commercially available nootropic drug. Although widely evaluated in the treatment of senile cognitive disorders and dyslexia, piracetam has also been assessed as a treatment for deficits associated with acute stroke. Data from a number of small, short term studies in patients treated within a few days of stroke suggest that piracetam is more effective than placebo for the treatment of functional deficits (Noble, S., Benfield, P., *CNS Drugs* **1998**, *9*, 497-511).

Some combination neuroprotectant therapies have been investigated in rodent ischaemia since the excitotoxic effects of glutamate can be blocked almost completely with GABA in cell culture, tissue slices, and in some animal models. On this basis a combination of muscimol and MK 801, an NMDA receptor antagonist, was investigated and shown to be effective (Lyden, P.D., Lonzo, L., *Stroke* **1994**, *25*, 189-196).

WO-A-99/25353 discloses the use of triazolo[4,3-b]pyridazine derivatives as benzodiazepine/$GABA_A$ modulators for the treatment of psychotic disorders and neurodegeneration.

WO-A-90/09174 discloses the use of the GABAergic agent Clomethiazole (chlormethiazole) in the prevention and/or treatment of neurodegeneration. Clomethiazole is thought to act through a GABAergic pathway, whereby it augments GABA's inhibitory effect on the CNS, giving the drug both hypnotic and neuroprotectant properties.

The clinical neuroprotectant profile of clomethiazole has been reviewed (Muckle, H., *IDrugs* **1999**, *2*, 184-193). A large-scale phase III trial has been completed in which clomethiazole was evaluated for its ability to reduce nerve damage in acute cerebrovascular ischaemia. A subgroup of patients who presented with large stroke, experienced a significant benefit. Of these (n = 545), 41% of treated patients were functionally independent after 90 days, compared to 30% of patients on placebo.

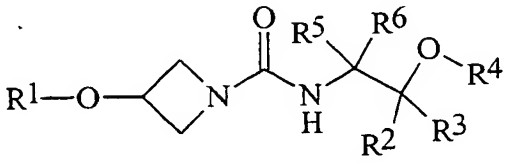
The effectiveness of this GABA modulator in rat (Snape, M.F., Baldwin, H.A., Cross, A.J., Green, A.R., *Neuroscience* **1993**, *53*, 837-844) and gerbil ischaemia (Cross, A.J., Jones, J.A., Baldwin, H.A., Green, A.R., *Br. J. Pharmacol.* **1991**, *104*, 406-411) has been demonstrated. The dose in the latter paradigm was 100 mg/kg, i.p.

Azetidine-1-carboxamides and the use of these compounds in the treatment of anxiety and all forms of epilepsy is described in International Patent Applications Nos. PCT/GB99/00224, PCT/GB99/00219 and PCT/GB99/00223.

There remains a medical need for new treatments for stroke and cerebrovascular disorders. The object of the present invention is to provide such treatments.

It has now been found that certain azetidine-1-carboxamides show unexpected neuroprotectant efficacy when compared to reference GABAergic agents. In particular, certain azetidine-1-carboxamides have been shown to potentiate the action of GABA in inhibiting neurones, and have also been shown to prevent the repetitive firing induced as a consequence of activation of glutamatergic mechanisms. Such compounds are found to be neuroprotective following acute cerebral ischaemia in rats and mice, and reduced ischaemia-induced CNS damage in *in vivo* models of focal ischaemia in both species.

According to the present invention, there is provided use of a compound of formula (I)



(I)

wherein:

R^1 is aryl; and

R^2, R^3, R^4, R^5 and R^6 which may be the same or different are selected from H, alkyl and aryl;

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for neuroprotection in a subject or for the treatment of cerebral ischaemia, central nervous system injury or eye diseases.

Reference in the present specification to an "alkyl" group means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl (including allyl) or alkynyl (including propargyl)) hydrocarbyl radical. Where cyclic or acyclic the alkyl group is preferably C_1 to C_{12}, more preferably C_1 to C_8 (such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, hexyl, heptyl, octyl). It will be appreciated therefore that the term "alkyl" as used herein includes alkyl (branched or unbranched), alkenyl (branched or unbranched), alkynyl (branched or unbranched), cycloalkyl, cycloalkenyl and cycloalkynyl. In a preferred embodiment, a cyclic alkyl group is preferably C_3 to C_{12}, more preferably C_5 to C_8 and an acyclic alkyl group is preferably C_1 to C_{10}, more preferably C_1 to C_6, more preferably methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, isobutyl or tertiary-butyl) or pentyl (including n-pentyl and iso-pentyl), more preferably methyl.

Reference in the present specification to an "aryl" group means a mono or bicyclic aromatic group, such as phenyl or naphthyl.

The alkyl and aryl groups may be substituted or unsubstituted. In one embodiment, only the alkyl and aryl groups defined above as R_1 to R_6 may be substituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 or 2 substituents. Substituents may include:

carbon containing groups such as

alkyl

aryl, arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

halogen atoms and halogen containing groups such as

haloalkyl (e.g. trifluoromethyl);

oxygen containing groups such as

alcohols (e.g. hydroxy, hydroxyalkyl, (aryl)(hydroxy)alkyl),

ethers (e.g. alkoxy, alkoxyalkyl, aryloxyalkyl),

oxo

aldehydes (e.g. carboxaldehyde),

ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl),

acids (e.g. carboxy, carboxyalkyl),

acid derivatives such as esters

(e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl)

and amides

(e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, arylaminocarbonyl);

nitrogen containing groups such as

amines (e.g. amino, mono- or di-alkylamino, aminoalkyl, mono- or di-alkylaminoalkyl),

azides,

nitriles (e.g. cyano, cyanoalkyl),

nitro;

sulphur containing groups such as

thiols, thioethers, sulphoxides and sulphones

(e.g. alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl);

and heterocyclic groups containing one or more, preferably one, heteroatom,

(e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl).

Preferred substituents include alkyl, aryl, halo, or an halogen-containing group such as trifluoromethyl.

As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO-.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine or chlorine radical.

The compounds of formula (I) may exist in a number of diastereomeric and/or enantiomeric forms. Unless otherwise stated, reference in the present specification to "a compound of formula (I)" is a reference to all stereoisomeric forms of the compound and includes a reference to the unseparated stereoisomers in a mixture, racemic or non-racemic, and to each stereoisomer in its pure form.

In a preferred embodiment of the present invention, a compound of formula (I) is the (*R*)-enantiomer of the compound of formula (I), substantially free of its (*S*)-enantiomer.

In the compounds of formula (I), preferably R^1 is a substituted or unsubstituted aryl group selected from phenyl, naphthyl and indanyl, more preferably R^1 is a substituted phenyl, naphthyl or indanyl, more preferably R^1 is a phenyl, naphthyl or indanyl having 1 to 3 substituents and, more preferably, R^1 is a phenyl, naphthyl or indanyl having 1 or 2

substituents. It is preferred that R^1 is a mono- or di-substituted phenyl or naphthyl, preferably a mono- or di-substituted phenyl, and most preferably a mono-substituted phenyl.

Where R^1 is a phenyl having 1 substituent, the phenyl group is preferably meta- or para-substituted. Where R^1 is a phenyl having 2 substituents, the phenyl group is preferably a 3,4-disubstituted phenyl or a 3,5-disubstituted phenyl, more preferably a 3,4-disubstituted phenyl.

Where R^1 is a naphthyl group it is preferred that R^1 is a 2-naphthyl group. Where R^1 is an indanyl group, it is preferred that R^1 is a 5-indanyl group.

Where R^1 is substituted, the preferred substituents are selected from chloro, fluoro, bromo, iodo, trifluoromethyl, tertiary-butyl, phenyl, CO_2Me and CN, preferably from chloro, fluoro, trifluoromethyl and tertiary-butyl, and more preferably from chloro, trifluoromethyl and tertiary-butyl.

Where R^1 is di-substituted, it is preferred that each substituent is independently selected from halo, preferably chloro and fluoro. Where R^1 is di-substituted, it is preferred that R^1 is substituted by two chloro groups or by one chloro and one fluoro group, and more preferably by two chloro groups.

The most preferred R^1 groups are selected from 3-chlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-tert-butylphenyl, 4-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 3,4-dichlorophenyl and 3,5-dichlorophenyl.

In the compounds of formula (I), R^2 is selected from H, alkyl (including hydroxyalkyl such as CH_2OH) and aryl. Preferably R^2 is selected from H and alkyl. Where R^2 is alkyl, R^2 is preferably methyl. Where R^2 is aryl, R^2 is preferably phenyl. Preferably R^2 is H or methyl. More preferably R^2 is methyl.

In the compounds of formula (I), R^3 is selected from H, alkyl (including hydroxyalkyl such as CH_2OH) and aryl. Preferably R^3 is selected from H and alkyl. Where R^3 is alkyl, R^3 is preferably methyl. Where R^3 is aryl, R^3 is preferably phenyl. Preferably R^3 is H or methyl.

In the compounds of formula (I), preferably R^4 is selected from H and alkyl (including hydroxyalkyl). Preferably R^4 is H or methyl. More preferably R^4 is H.

In the compounds of formula (I), preferably R^5 is selected from H and alkyl (including carboxy, alkoxycarbonyl and aminocarbonyl). R^5 is preferably H or methyl. More preferably R^5 is H.

In the compounds of formula (I), preferably R^6 is selected from H and alkyl (including carboxy, alkoxycarbonyl and aminocarbonyl). R^6 is preferably H or methyl. More preferably R^6 is H.

In one embodiment of the invention R^2, R^3, R^4, R^5 and R^6 are independently selected from H and alkyl.

In a further embodiment of the invention, R^2 is H and R^3 is methyl or R^2 is methyl and R^3 is H.

In a further embodiment of the invention R^4, R^5 and R^6 are H.

In the compounds of formula (I), R^2 and R^4 may optionally be linked by a saturated divalent radical chain of carbon atoms to form a 5, 6 or 7 membered ring, preferably a 5 membered ring, such as tetrahydrofuran.

In the compounds of formula (I), R^2 and R^3 may optionally be linked by a saturated divalent radical chain of carbon atoms to form a 5, 6 or 7 membered ring, preferably a 6 membered ring, such as cyclohexane.

In the compounds of formula (I), R^2 and R^5 may optionally be linked by a saturated divalent radical chain of carbon atoms to form a 5, 6 or 7 membered ring, preferably a 6 membered ring, such as cyclohexane.

In the compounds of formula (I) wherein any of R_1 to R_6, and particularly R_1, is selected from aryl substituted by two alkyl groups, particularly two alkyl groups which are in adjacent ring

positions on said aryl ring, then said alkyl groups may be cyclised to form a 5, 6 or 7 membered ring, preferably a 5 or 6 membered ring, more preferably a 5 membered ring.

Particularly preferred compounds are as follows:-

Chirality	R^1	R^2	R^3	R^4	R^5	R^6
R	4-(Me_3C)-C_6H_4	H	Me	H	H	H
R	4-Cl-C_6H_4	H	Me	H	H	H
S	4-Cl-C_6H_4	Me	H	H	H	H
-	4-Cl-C_6H_4	Me	Me	H	H	H
R	4-F-C_6H_4	H	Me	H	H	H
R	3,4-Cl_2-C_6H_3	H	Me	H	H	H
R	4-CF_3-C_6H_4	H	Me	H	H	H
R	3-CF_3-C_6H_4	H	Me	H	H	H
R	3-Cl-C_6H_4	H	Me	H	H	H
R	3,5-Cl_2-C_6H_3	H	Me	H	H	H

Of these, the preferred compounds are: (*R*)-3-(4-*tert*-butylphenoxy)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, (*R*)-3-(4-chlorophenoxy)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, (*S*)-3-(4-chlorophenoxy)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, (*R*)-3-(3,4-dichlorophenoxy)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, (*R*)-3-(4-trifluoromethyl)phenoxy-*N*-(2-hydroxypropyl)azetidine-1-carboxamide and (*R*)-3-(3-trifluoromethyl)phenoxy-*N*-(2-hydroxypropyl)azetidine-1-carboxamide.

According to a further aspect of the present invention there is provided a method of neuroprotection comprising administration to a subject in need of such treatment an effective dose of the compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof.

According to a further aspect of the present invention there is provided a method of treatment of cerebral ischaemia, central nervous system injury or eye diseases comprising

administration to a subject in need of such treatment an effective dose of the compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof.

The present invention may be employed in respect of a human or animal subject, more preferably a mammal, more preferably a human subject.

As used herein, the term "treatment" as used herein includes prophylactic treatment.

As used herein, the term "prodrug" means any pharmaceutically acceptable prodrug of the compound of formula (I). For example, the compound of formula (I) may be prepared in a prodrug form wherein a free –OH group is derivatised (for example, via an ester, amide or phosphate bond) with a suitable group (the group may contain, for example, an alkyl, aryl, phosphate, sugar, amine, glycol, sulfonate or acid function) which is suitably labile so as it will be removed / cleaved (eg. by hydrolysis) to reveal the compound of formula (I) sometime after administration or when exposed to the desired biological environment.

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula (I). Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like. Particularly preferred are hydrochloric, hydrobromic, phosphoric, sulfuric and methanesulfonic acids, and most particularly preferred is the methanesulfonate salt. Acceptable base salts include alkali metal (e.g. sodium, potassium), alkaline earth metal (e.g. calcium, magnesium) and aluminium salts.

As used herein, the term "substantially free of its (*S*)-enantiomer" means that the medicament or therapeutic composition comprising the compound of formula (I) used according to the present invention contains a greater proportion of the (*R*)-enantiomer of the compound of formula (I) in relation to the (*S*)-enantiomer of the compound of formula (I). In a preferred embodiment of the present invention the term "substantially free of its

(*S*)-enantiomer", as used herein, means that the composition contains at least 90 % by weight of the (*R*)-enantiomer and 10 % by weight or less of the (*S*)-enantiomer. In a further preferred embodiment, the term "substantially free of its (*S*)-enantiomer" means that the composition contains at least 99 % by weight of the (*R*)-enantiomer and 1 % or less of the (*S*)-enantiomer. In another preferred embodiment, the term "substantially free of its (*S*)-enantiomer" means that the composition contains 100 % by weight of the (*R*)-enantiomer. The above percentages are based on the total amount of compound of formula (I) present in the medicament or therapeutic composition used according to the present invention.

The diseases, disorders and medical treatments/procedures to which the present invention is directed are:

Cerebral Ischaemia,

including transient ischaemic attack, stroke (thrombotic stroke, ischaemic stroke, embolic stroke, haemorrhagic stroke, lacunar stroke), subarachnoid haemorrhage, cerebral vasospasm, neuroprotection for stroke, peri-natal asphyxia, drowning, carbon monoxide poisoning, cardiac arrest and subdural haematoma;

Central Nervous System Injury,

including traumatic brain injury, neurosurgery (surgical trauma), neuroprotection for head injury, raised intracranial pressure, cerebral oedema, hydrocephalus and spinal cord injury; and

Eye Diseases,

including drug-induced optic neuritis, cataract, diabetic neuropathy, ischaemic retinopathy, retinal haemorrhage, retinitis pigmentosa, acute glaucoma, chronic glaucoma, macular degeneration, retinal artery occlusion and retinitis.

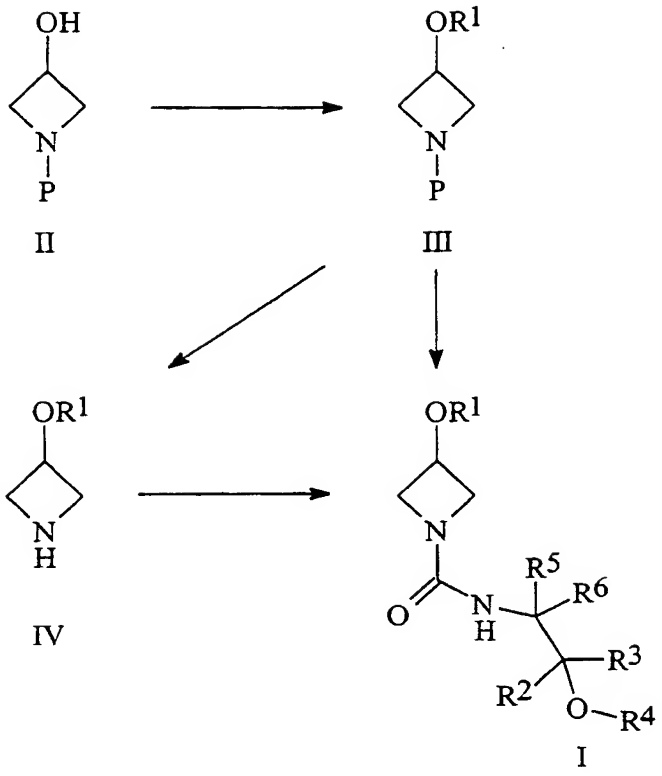
Additionally, the compound of formula (I) may also be used to potentiate the effects of other treatments, for example to potentiate the neuroprotective effects of brain derived nerve growth factor.

The invention is particularly directed to the treatment of cerebral ischaemia and central nervous system injury. The invention is also particularly directed to the treatment of post-asphyxial brain damage in new-born subjects.

The compound of formula (I) may be used in combination with one or more additional drugs useful in the treatment of the disorders mentioned above, the components being in the same formulation or in separate formulations for administration simultaneously or sequentially.

Compounds of formula (I) may be prepared according to the reaction scheme (where P is a nitrogen protecting group). R^1, R^2, R^3, R^4, R^5, R^6 are as previously defined. The 3-(aryloxy)azetidine (III) may be formed by reaction of the azetidinol (II) either with an arylalkanol (R^1OH) and diethylazo dicarboxylate and triphenyl phosphine or with a substituted aryl fluoride (R^1F) and a strong base such as sodium hydride. Formation of the azetidine (IV) is achieved by reaction of (III) with a suitable nitrogen deprotection agent. For example, if P is a diphenylmethyl group, then deprotection may be carried out by treatment with 1-chloroethyl chloroformate followed by methanol. The urea (I) is formed by reaction of azetidine (IV) with an N-alkylisocyanate or an N-alkylcarbamoyl chloride and a base such as triethylamine or potassium carbonate. Alternatively, the urea may be prepared directly from the azetidine (III) without isolation of an intermediate such as the secondary amine (IV). For example, when P is a diphenylmethyl group, azetidine (III) may be treated with phosgene followed by alkylamine $R^4O.CR^2R^3.CR^5R^6.NH_2$ to give urea (I) directly.

Reaction Scheme



The invention further provides a pharmaceutical composition comprising an effective amount of the compound of formula (I) in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining an effective amount of the compound of formula (I) with a pharmaceutically acceptable carrier or excipient.

To further increase efficacy, the composition may contain components such as dextrans or cyclodextrins or ether derivatives thereof, which aid stability and dispersion, and decrease metabolism of the active ingredient.

For compositions in which the pharmaceutically acceptable carrier comprises a cyclodextrin or an ether derivative thereof, the active ingredient is intimately mixed with an aqueous solution of the cyclodextrin or ether derivative thereof, with optional addition of further pharmaceutically acceptable ingredients before, during or after said mixing. The thus obtained solution is optionally lyophilized, and the lyophilized residue is optionally reconstituted with water.

In an embodiment of the present invention, the composition further comprises a buffer system, an isotonizing agent and water.

Compounds of formula (I) may be administered in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use including transmucosal and transdermal use, for example a cream, ointment, gel, aqueous or oil solution or suspension, salve, patch or plaster; for nasal use, for a example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example a finely divided powder or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oil solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients, using standard techniques well known to those skilled in the art of pharmacy. Preferably, the compound is administered orally.

For oral administration, the compounds of formula (I) will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose,

while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of formula (I) generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

It will be appreciated that the dosage levels used may vary over quite a wide range depending upon the compound used, the severity of the symptoms exhibited by the patient and the patient's body weight.

The invention will now be described in detail with reference to the following pharmacological examples. It will be appreciated that the examples are intended to illustrate and not to limit the scope of the present invention.

EXAMPLES

Synthetic Examples

Preparation of 1-(Diphenylmethyl)-3-azetidinol

This compound was prepared according to the method of Anderson and Lok (*J. Org. Chem.*, **1972**, *37*, 3953, the disclosure of which is incorporated herein by reference), m.p. 111-112 °C (lit. m.p. 113 °C).

Preparation of 3-(4-*tert*-Butylphenoxy)-1-(diphenylmethyl) azetidine (1)

Triphenylphosphine (13.11 g, 50.0 mmol) was added to a stirred solution of 1-(diphenylmethyl)-3-azetidinol (11.97 g, 50.0 mmol) and 4-*tert*-butylphenol (7.50 g, 50.0 mmol) in acetonitrile (200 mL). Diethyl azodicarboxylate (7.9 mL, 8.7 g, 50.0 mmol) was added dropwise to the solution with water cooling. The suspension was heated under reflux for 4 h, the solution allowed to cool and concentrated *in vacuo*. The gum was suspended in ether (200 mL), and the suspension was refrigerated overnight. The precipitated triphenylphosphine oxide was filtered off and washed with ether, and the combined filtrate and washings were concentrated. The solid residue was dissolved in dichloromethane (200 mL), and the solution was washed with 1-N sodium hydroxide (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by chromatography [SiO_2; ethyl acetate-hexane (1:4)] and triturated with cyclohexane to give the title compound (9.39 g, 51 %) as a white solid, m.p. 126-127 °C. Found: C, 83.9; H, 7.9; N, 3.75. $C_{26}H_{29}NO$ requires C, 84.1; H, 7.9; N, 3.8%.

Example 1. (*R*)-3-(4-*tert*-Butylphenoxy)-N-(2-hydroxypropyl) azetidine-1-carboxamide (2)

A solution of compound (1) (2.30 g, 6.19 mmol) in dichloromethane (25 mL) was treated with phosgene solution (*ca.* 20 wt. % in toluene; 3.28 mL, 6.2 mmol) with water cooling. The solution was stirred for 1 h, cooled to 0 °C, and (*R*)-1-amino-2-propanol (1.08 mL, 1.03 g, 13.7 mmol) added dropwise. The solution was stirred for 18 h. Dichloromethane (25 mL) was added, and the solution was washed with 1-M HCl (25 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by chromatography [SiO_2; MeOH-ethyl acetate-hexane (0:2:3→0:1:0→1:9:0)] and triturated with ether to give the title compound (1.15 g, 61 %) as a white solid, m.p. 98-99 °C. Found: C, 66.5; H, 8.8; N, 9.1. $C_{17}H_{26}N_2O_3$ requires C, 66.6; H, 8.55; N, 9.1 %.

Example 2. (*R*)-3-(4-Chlorophenoxy)-*N*-(2-hydroxypropyl) azetidine-1-carboxamide (3)

This product was prepared from 3-(4-chlorophenoxy)-1-(diphenylmethyl)azetidine (as described in US-4,956,359, the disclosure of which is incorporated herein by reference) and (*R*)-1-amino-2-propanol using the procedure described for compound (2) (69 % yield), m.p. 104-105 °C. Found: C, 54.9; H, 6.0; N, 9.7. $C_{13}H_{17}N_2O_3$ requires C, 54.8; H, 6.0; N, 9.8 %.

Example 3. (*S*)-3-(4-Chlorophenoxy)-*N*-(2-hydroxypropyl) azetidine-1-carboxamide (4)

This product was prepared from from 3-(4-chlorophenoxy)-1-(diphenylmethyl)azetidine and (*S*)-1-amino-2-propanol using the procedure described for compound (2) (57 % yield), m.p. 104-105 °C. Found: C, 54.7; H, 6.0; N, 9.7. $C_{13}H_{17}N_2O_3$ requires C, 54.8; H, 6.0; N, 9.8%.

Example 4. 3-(4-Chlorophenoxy)-*N*-(2-hydroxy-2-methylpropyl) azetidine-1-carboxamide (5)

This product was prepared from 3-(4-chlorophenoxy)-1-(diphenylmethyl)azetidine and 1-amino-2-methyl-2-propanol using the procedure described for compound (2) (35 % yield), m.p. 121-122 °C. Found: C, 56.0; H, 6.6; N, 8.85. $C_{14}H_{19}N_2O_3$ requires C, 56.3; H, 6.4; N, 9.4%.

Example 5. (*R*)-3-(4-Fluorophenoxy)-*N*-(2-hydroxypropyl) azetidine-1-carboxamide (6)

This product was prepared from 3-(4-fluorophenoxy)-1-(diphenylmethyl)azetidine (as described in US-4,956,359, the disclosure of which is incorporated herein by reference) and (*R*)-1-amino-2-propanol using the procedure described for compound (2) (76 % yield), m.p. 112-114 °C. Found: C, 58.3; H, 6.4; N, 10.4. $C_{13}H_{17}FN_2O_3$ requires C, 58.2; H, 6.4; N, 10.4%.

Example 6. (*R*)-3-(3,4-Dichlorophenoxy)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (7)

This product was prepared from 3-(3,4-dichlorophenoxy)-1-(diphenylmethyl) azetidine (as described in US-4,956,359, the disclosure of which is incorporated herein by reference) and (*R*)-1-amino-2-propanol using the procedure described for compound (2) (88 % yield), m.p. 83-84 °C. Found: C, 49.8; H, 5.05; N, 8.35. $C_{13}H_{17}N_2O_3$ requires C, 48.9; H, 5.05; N, 8.8%.

Example 7. (*R,S*)-3-(4-Chlorophenoxy)-*N*-(2-hydroxypropyl)azetidine-1-carboximide (8)

This product was prepared from 3-(4-chlorophenoxy)-1-(diphenylmethyl)azetidine and (d,l)-1-amino-2-propanol using the procedure described for compound (2) (81% yield), m.p. 104-105°C. Found: C, 55.1; H, 6.1; N, 9.8. $C_{13}H_{17}N_2O_3$ requires C, 54.8; H, 6.0; N, 9.8%.

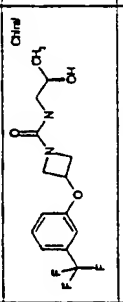
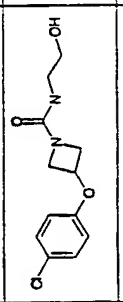
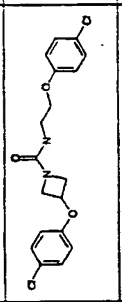
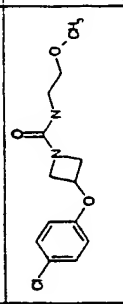
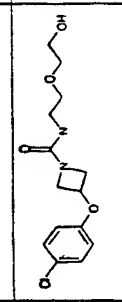
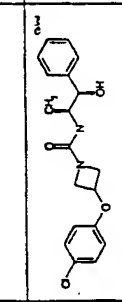
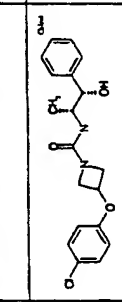
Example 8. (*R*)-3-(4-(Trifluoromethyl)phenoxy)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (9)

This product was prepared from 3-(4-trifluoromethyl)phenoxy)-1-(diphenylmethyl)azetidine and (*R*)-1-amino-2-propanol using the procedure described for compound (2) (60% yield), m.p. 112.5-113 °C. Found; C, 52.9; H, 5.4; N, 8.7. $C_{14}H_{17}F_3N_2O_3$ requires C, 52.8; H, 5.4; N, 8.8%.

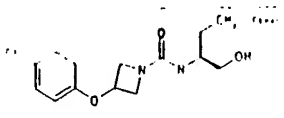
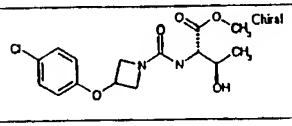
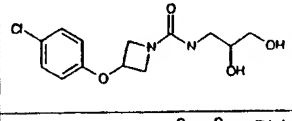
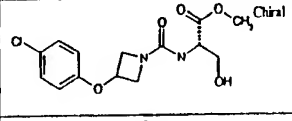
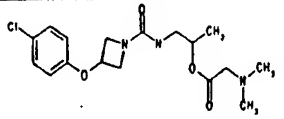
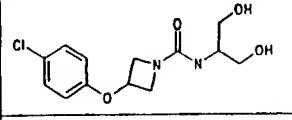
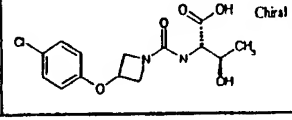
Examples 9 to 58 (see Table 1)

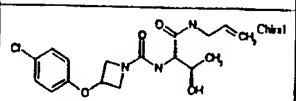
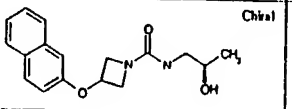
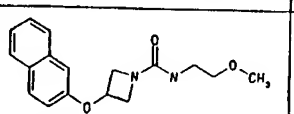
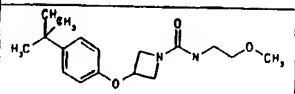
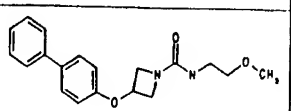
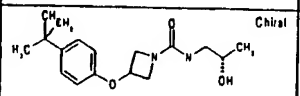
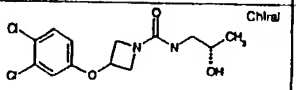
These products were prepared using the procedure described for compound (2).

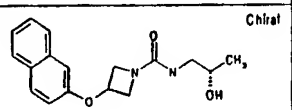
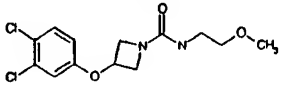
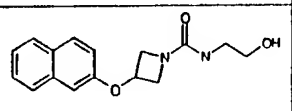
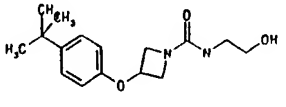
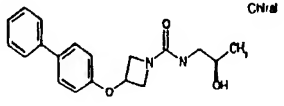
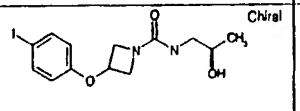
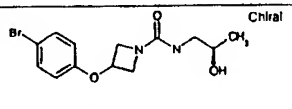
Table 1

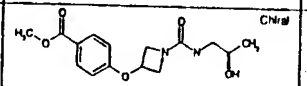
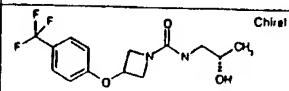
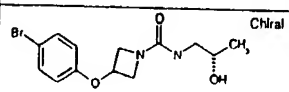
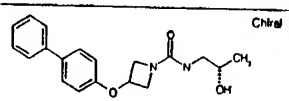
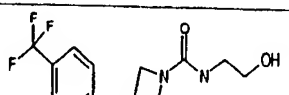
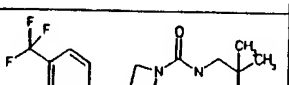
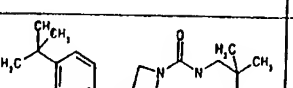
Example No	Compound No	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
9	10		C14H17F3N2O3	318.30	86.00	52.81	5.34	8.73	52.83	5.38	8.80	
10	11		C12H15ClN2O3	270.72								
11	12		C18H18Cl2N2O3	381.26								
12	13		C13H17ClN2O3	284.75								
13	14		C14H19ClN2O4	314.77								
14	15		C19H21ClN2O3	360.84								
15	16		C19H21ClN2O3	360.84								

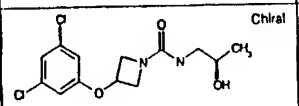
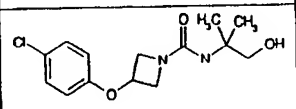
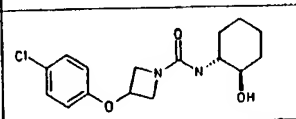
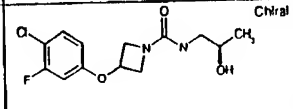
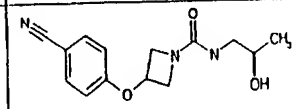
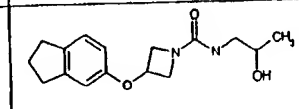
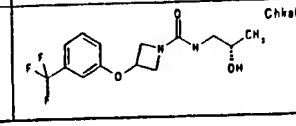
Example No	Compound No	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
16	17		C15H19ClN2O3	310.78								
17	18		C15H19ClN2O3	310.78								
18	19		C13H17ClN2O3	284.75								
19	20		C13H17ClN2O3	284.75								
20	21		C18H19ClN2O3	346.82								
21	22		C17H23ClN2O3	338.84								
22	23		C14H19ClN2O3	298.77								

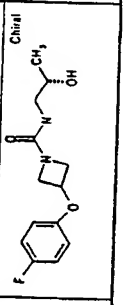
Example No	Compound No	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
23	24		C14H19ClN2O3	298.77								
24	25		C15H19ClN2O5	342.78								
25	26		C13H17ClN2O4	300.74								
26	27		C14H17ClN2O5	328.75								
27	28		C17H24ClN3O4	369.85								
28	29		C13H17ClN2O4 (0.5H2O)	300.74	119-121	50.60	5.85	8.97	50.41	5.86	9.04	
29	30		C14H17ClN2O5 (0.25H2O)	328.75	123-124 dec	50.69	5.34	7.97	50.46	5.29	8.41	

Example No	Compound No	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
30	31		C17H22ClN3O4	367.84	>50 dec							a
31	32		C17H20N2O3	300.36	136-137	68.03	6.62	8.76	67.98	6.71	9.32	
32	33		C17H20N2O3	300.36	105-105.5	68.05	6.70	9.18	67.98	6.71	9.32	
33	34		C17H26N2O3	306.41	97-98	66.75	8.56	8.81	66.64	8.55	9.14	
34	35		C19H22N2O3	326.40	118.00	69.87	6.82	8.55	69.92	6.79	8.68	
35	36		C17H26N2O3	306.41	99-100	66.21	8.55	9.10	66.64	8.55	9.14	
36	37		C13H16Cl2N2O3	319.19	86-89	49.16	4.99	8.40	48.92	5.05	8.77	

Example No	Compound No	Structure	Formula	MWt	mp	Clound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
37	38	 Chiral	C17H20N2O3	300.36	136-138	67.33	6.65	8.93	66.98	6.78	9.19	
38	39		C13H16Cl2N2O3	319.19	105.5-106	49.04	4.98	8.60	48.92	5.05	8.77	
39	40		C16H18N2O3	286.33	128-128.5	66.84	6.33	9.67	67.12	6.34	9.78	
40	41		C16H24N2O3	292.38	111-111.5	65.54	8.34	9.49	65.73	8.27	9.58	
41	42	 Chiral	C19H22N2O3	326.40	156-157	69.69	6.74	8.39	69.92	6.79	8.58	
42	43	 Chiral	C13H17IN2O3	376.20	118-120	42.18	4.54	7.21	41.51	4.55	7.44	
43	44	 Chiral	C13H17BrN2O3	329.20	110-111	47.90	5.24	8.42	47.43	5.20	8.51	

Example No	Compound No	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
44	45		C15H20N2O5	308.34	243-244	58.46	6.56	9.05	58.43	6.54	9.08	
45	46		C14H17F3N2O3	318.30	111-111.5	53.09	5.46	8.72	52.81	5.38	8.80	
46	47		C13H17BrN2O3	329.20	108-110	48.09	5.18	8.16	47.43	5.20	8.51	
47	48		C19H22N2O3 (0.25 H2O)	326.40	157-158	69.19	6.84	8.65	68.97	6.85	8.47	
48	49		C13H15F3N2O3	304.27	113.5-114.5	51.37	5.01	9.06	51.32	4.97	9.20	
49	50		C15H19F3N2O3	332.33	136-137	54.09	5.94	8.40	54.21	5.76	8.43	
50	51		C18H28N2O3	320.44	104.5-106	67.36	9.04	8.73	67.47	8.81	8.74	

Example No	Compound No	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
51	52	 Chiral	C13H16Cl2N2O3	319.19	121-121.5	48.97	4.98	8.87	48.92	5.05	8.77	
52	53		C14H19ClN2O3 (0.5 H2O)	298.77	153.00	54.69	6.28	9.26	54.63	6.55	9.10	
53	54		C16H21ClN2O3	324.81	154-155.5	59.12	6.58	8.64	59.17	6.52	8.62	
54	55	 Chiral	C13H16ClFN2O3	302.74	118.5-120.5	51.62	5.37	9.14	51.58	5.33	9.25	
55	56		C14H17N3O3	275.31								b
56	57		C16H22N2O3	290.37								c
57	58	 Chiral	C14H17F3N2O3	318.30		52.91	5.42	8.72	52.83	5.38	8.80	

Example No	Compound No	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
58	59		C13H17FN2O3	268.29		58.31	6.44	10.39	58.20	6.39	10.44	

Footnotes to Table 1.

Footnote a: IR: 3300, 2927, 1638, 1545, 1490, 1466, 1378, 1242, 1091, 825, 665 cm^{-1}.

Footnote b: IR: 3519, 3271, 2926, 2855, 2233, 1624, 1606, 1506, 1458, 1397, 1260, 1171, 1126, 832, 550 cm^{-1}.

Footnote c: IR: 3350, 2925, 2854, 1627, 1549, 1488, 1469, 1397, 1374, 1326, 1273, 1149, 1137, 1088, 803 cm^{-1}.

Testing Procedures

Rat transient middle cerebral artery occlusion (MCAo) ischaemia model

This model of middle cerebral artery occlusion used relies on an intraluminal filament technique in the rat (Zhao Q. *et al.*, *Acta Physiol. Scand.* **1994**, *152*, 349-350). Male Lister Hooded rats were used in these experiments and were divided into three groups (Group 1: vehicle; Group 2: chlomethiazole (CMZ); Group 3: a compound of formula (I)). The sample size in each was 11 to 15. The animal was anaesthetised and the carotid artery exposed. A heat-rounded dermalon suture (3/0) of a specified diameter was introduced into the ligated carotid artery, past the bifurcations of the external and common carotid, the internal carotid and the pterygopalatine artery, into the intracranial circulation. The filament then lodged in the narrow proximal anterior carotid occluding the middle cerebral artery. After 90 min. of middle cerebral artery occlusion, the filament was removed, allowing re-circulation.

22.5 h following reperfusion, the animal was perfused *via* the transaortic route, using 200 ml of a 4 percent solution of tetrazolium chloride warmed to 37° C. Following perfusion, the brain was removed and immersion fixed in 10 percent formalin/saline for at least 48 h. Following fixation, the brain was sliced into 0.5 mm sections on a vibroslice. Using this technique, viable tissue was stained dark red and infarcted tissue remains unstained. The area of infarction on each section was measured, and the total volume of infarction in the hemisphere, cortex and striatum computed, using the Kontron image analysis system.

Mouse permanent middle cerebral artery occlusion ischaemia model

Adult male C57Bl mice (20-25 g, n = 10 per group) were administered a compound of formula (I) (10 mg/kg) or vehicle (60% PEG400 in water) i.p. 30 minutes prior to middle cerebral artery (MCA) occlusion. Under halothane anaesthesia (1.5% halothane in nitrous oxide: oxygen (70:30)), a small craniectomy was made to expose the left MCA. The distal portion of the MCA was occluded by electrocoagulation. The incision site was sutured and anaesthetics withdrawn. 24 h following MCA occlusion, the mouse was euthanised, the brain removed and immersed in 4% tetrazolium chloride to visualise the area of infarction (Backhaus C. *et al.*, *J. Pharm Methods* **1992**, *27*, 27-32). Brains were then stored in 10% formalin/saline. The area of infarction as visible on the cortical surface was then computed using a PC digital imaging system (KS300, Imaging Associates, UK). Data generated is absolute area of infraction in mm^2 for each animal. Mean infarct areas were compared by unpaired t-tests with significance taken at $p < 0.05$.

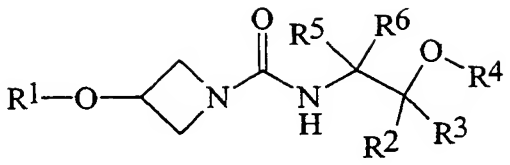
The experimental results are displayed in Figures 1 and 2 which show the effects of (i) vehicle; and (ii) 60 mg/kg i.p. of compound 10 or compound 58 on infarction after permanent middle cerebral artery occlusion.

Figure 1 shows that compound 10 exhibits significant neuroprotection at a dose of 60 mg/kg i.p. in the mouse permanent MCAo model.

Figure 2 shows that compound 58 exhibits significant neuroprotection at a dose of 60 mg/kg i.p. in the mouse permanent MCAo model.

CLAIMS

1. Use of a compound of formula (I)



(I)

wherein

R^1 is aryl; and

R^2, R^3, R^4, R^5 and R^6 which may be the same or different are selected from H, alkyl and aryl;

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for neuroprotection in a subject or for the treatment of cerebral ischaemia, central nervous system injury or eye diseases.

2. A use according to claim 1 wherein R^1 is a substituted or unsubstituted aryl group selected from phenyl, naphthyl and indanyl.

3. A use according to claim 1 or 2 wherein R^1 has 1, 2 or 3 substituent groups.

4. A use according to claim 1 wherein R^1 is a para-substituted phenyl group.

5. A use according to claim 1 wherein R^1 is a meta-substituted phenyl group.

6. A use according to claim 1 wherein R^1 is a 3,4-disubstituted phenyl group or a 3,5-disubstituted phenyl group.

7. A use according to any preceding claim wherein R^1 is substituted by one or more groups selected from chloro, fluoro, bromo, iodo, trifluoromethyl, tertiary-butyl, phenyl, CO_2Me and CN.

8. A use according to claim 1 wherein R^1 is selected from 3-chlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-tert-butylphenyl, 4-(trifluoromethyl)phenyl and 3-(trifluoromethyl)phenyl.

9. A use according to claim 3 or claim 6 wherein R^1 has 2 substituent groups each of which are independently selected from halo.

10. A use according to claim 1 wherein R^1 is 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl or 3,5-dichlorophenyl.

11. A use according to any one of claims 1 to 10 wherein R^2, R^3, R^4, R^5 and R^6 are independently selected from H and alkyl.

12. A use according to any one of claims 1 to 11 wherein R^2, R^3, R^4, R^5 and R^6 are independently selected from H and methyl.

13. A use according to any one of claims 1 to 11 wherein one or both of R^2 and R^3 are hydroxyalkyl.

14. A use according to any one of claims 1 to 10 wherein one or both of R^2 and R^3 are phenyl.

15. A use according to any preceding claim wherein R^4 is hydroxyalkyl.

16. A use according to any preceding claim wherein R^5 and R^6 are independently selected from carboxy, alkoxycarbonyl and aminocarbonyl.

17. A use compound according to any one of claims 1 to 14 wherein R^4, R^5 and R^6 are hydrogen

18. A use according to any one of claims 1 to 10 wherein R^2 is hydrogen and R^3 is methyl or R^2 is methyl and R^3 is hydrogen.

19. A use according to claim 1 wherein the compound is selected from (*R*)-3-(4-*tert*-butylphenoxy)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, (*R*)-3-(4-chlorophenoxy)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, (*S*)-3-(4-chlorophenoxy)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(4-chlorophenoxy)-*N*-(2-hydroxy-2-methylpropyl)azetidine-1-carboxamide, (*R*)-3-(4-fluorophenoxy)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, (*R*)-3-(4-trifluoromethyl)phenoxy-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, (*R*)-3-(3,4-dichlorophenoxy)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, (*R*)-3-(3-trifluoromethyl)phenoxy-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, (*R*)-3-(3-chlorophenoxy)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide and (R)-3-(3,5-dichlorophenoxy)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide.

20. A use according to any one of claims 1 to 10 wherein R^2 and R^4 are linked by a saturated divalent radical chain of carbon atoms to form a 5, 6 or 7 membered ring.

21. A use according to any one of claims 1 to 10 wherein R^2 and R^3 are linked by a saturated divalent radical chain of carbon atoms to form a 5, 6 or 7 membered ring.

22. A use according to any one of claims 1 to 10 wherein R^2 and R^5 are linked by a saturated divalent radical chain of carbon atoms to form a 5, 6 or 7 membered ring.

23. A use according to any preceding claim wherein said medicament comprises a pharmaceutically acceptable carrier and as active ingredient an effective amount of a compound of formula (I).

24. A use according to claim 23 wherein said carrier comprises a cyclodextrin or an ether derivative thereof.

25. A use according to any preceding claim wherein the medicament further comprises a buffer system, an isotonizing agent and water.

26. Use according to any of preceding claim wherein the compound of formula (I) is in combination with one or more additional drugs useful in neuroprotection or the treatment

of cerebral ischaemia, central nervous system injury or eye diseases, the components being in the same formulation or in separate formulations for administration simultaneously or sequentially.

27. A method of neuroprotection comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) as defined in any of claims 1 to 22, or a pharmaceutically acceptable salt or prodrug thereof.

28. A method of treatment of cerebral ischaemia, central nervous system injury or eye diseases comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) as defined in any of claims 1 to 22, or a pharmaceutically acceptable salt or prodrug thereof.

29. A method according to claim 27 or 28 wherein the compound of formula (I) is administered in the form as set out in any of claims 23, 24, 25 or 26.

Figure 1

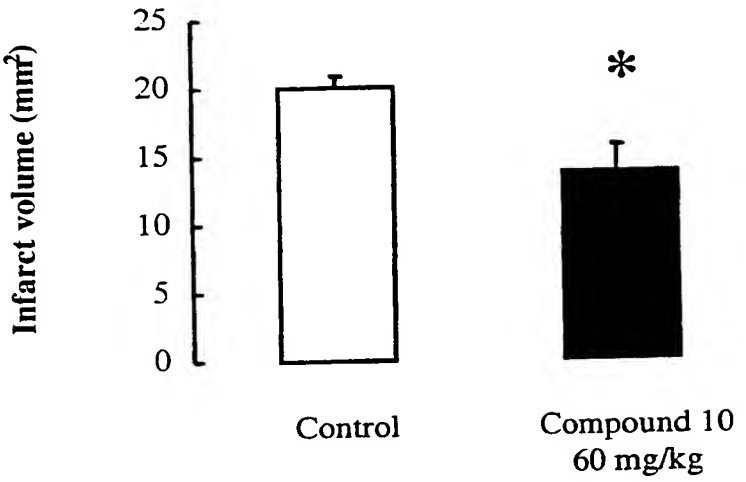
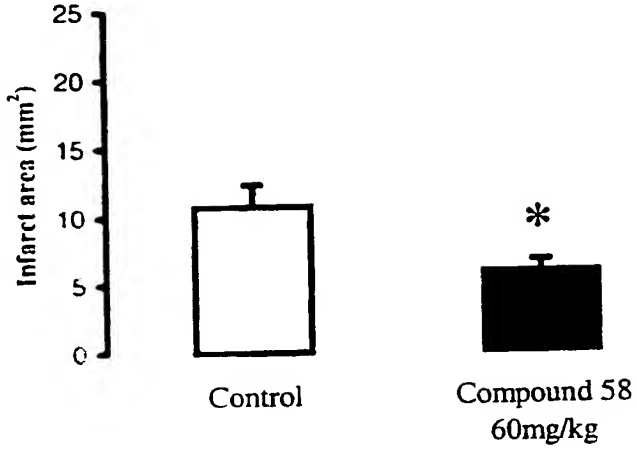


Figure 2



INTERNATIONAL SEARCH REPORT

tional Application No
PCT/GB 00/02840

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/397 C07D205/04 C07D405/12 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 102 740 A (ROBINS CO INC A H) 14 March 1984 (1984-03-14) claims	1-29
A	EP 0 194 112 A (ROBINS CO INC A H) 10 September 1986 (1986-09-10) claims	1-29
P,X	WO 99 37614 A (CEREBRUS LTD ;ADAMS DAVID REGINALD (GB); CLIFFE IAN ANTHONY (GB);) 29 July 1999 (1999-07-29) claims	1-29

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 2000	25/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Chouly, J

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/02840

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0102740 A	14-03-1984	US 4505907 A	19-03-1985
		AT 23329 T	15-11-1986
		AU 553472 B	17-07-1986
		AU 1459883 A	08-03-1984
		CA 1185983 A	23-04-1985
		CS 8306141 A	13-06-1985
		DE 3367385 D	11-12-1986
		DK 398783 A,C	03-03-1984
		EG 16473 A	30-12-1990
		ES 523194 D	16-04-1985
		ES 8504697 A	16-07-1985
		ES 537668 D	16-09-1985
		ES 8600234 A	01-01-1986
		FI 833126 A,B,	03-03-1984
		GR 79337 A	22-10-1984
		HK 47587 A	26-06-1987
		HU 189740 B	28-07-1986
		IE 55770 B	16-01-1991
		IN 161940 A	27-02-1988
		IN 161222 A	24-10-1987
		JP 1772175 C	14-07-1993
		JP 4052264 B	21-08-1992
		JP 60001161 A	07-01-1985
		KE 3696 A	13-03-1987
		KR 9005131 B	20-07-1990
		NO 833135 A,B,	05-03-1984
		NZ 205448 A	30-08-1985
		PH 20572 A	18-02-1987
		PL 243555 A	27-08-1984
		PT 77281 A,B	01-10-1983
		YU 170483 A	30-04-1986
		ZA 8304410 A	28-03-1984
EP 0194112 A	10-09-1986	AT 52915 T	15-06-1990
		AU 599585 B	26-07-1990
		AU 5388786 A	04-09-1986
		CY 1724 A	06-05-1994
		DE 3671369 D	28-06-1990
		DK 90086 A	29-08-1986
		FI 860847 A,B,	29-08-1986
		GR 860549 A	24-06-1986
		HK 83893 A	20-08-1993
		IE 58943 B	01-12-1993
		JP 1965813 C	25-08-1995
		JP 6099306 B	07-12-1994
		JP 61210031 A	18-09-1986
		NZ 215313 A	26-02-1990
		PH 25455 A	01-07-1991
		PT 82117 A,B	01-03-1986
		SG 50893 G	09-07-1993
		US 4956359 A	11-09-1990
		ZA 8601210 A	28-10-1987
		AU 599312 B	19-07-1990
		AU 5388886 A	04-09-1986
		CA 1294274 A	14-01-1992
		DK 36893 A	29-03-1993
		DK 90186 A	29-08-1986
		ES 552472 D	01-05-1987

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/02840

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0194112 A		ES 8802300 A	16-07-1988
		GR 860531 A	24-06-1986
		IL 77995 A	30-06-1989
		IN 162808 A	09-07-1988
		JP 1965814 C	25-08-1995
		JP 6099386 B	07-12-1994
		JP 61205254 A	11-09-1986
		NZ 215312 A	26-02-1990
		PH 25525 A	24-07-1991
		PT 82118 A,B	01-03-1986
		US 5183902 A	02-02-1993
		US 5151418 A	29-09-1992
		US 5068231 A	26-11-1991
		ZA 8601215 A	29-10-1986
WO 9937614 A	29-07-1999	AU 2178199 A	09-08-1999

Form PCT/ISA/210 (patent family annex) (July 1992)